

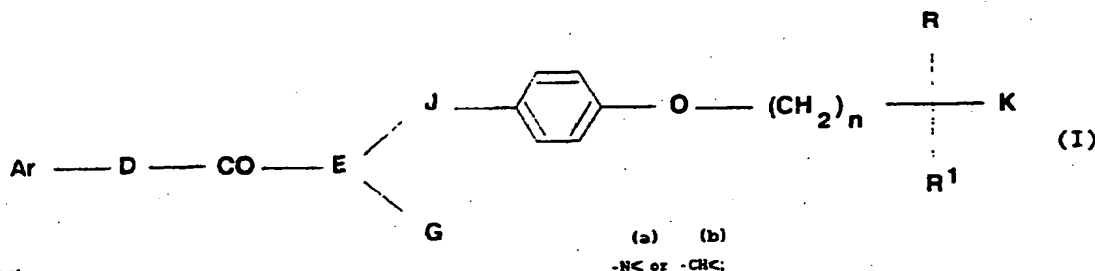
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> C07C 275/34, 275/30, 275/28 A61K 31/19, 31/17 C07C 273/18	<b>A1</b>	<b>(11) International Publication Number:</b> WO 92/10468  <b>(43) International Publication Date:</b> 25 June 1992 (25.06.92)
<b>(21) International Application Number:</b> PCT/GB91/02195  <b>(22) International Filing Date:</b> 11 December 1991 (11.12.91)  <b>(30) Priority data:</b> 9027023.2 12 December 1990 (12.12.90) GB  <b>(71) Applicants (for all designated States except US):</b> THE WELLCOME FOUNDATION LIMITED [GB/GB]; Unicorn House, 160 Euston Road, London NW1 2BP (GB). THE UNIVERSITY OF SOUTH CAROLINA [US/US]; Osborne Administration Building, Columbia, SC 29208 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> FRANZMANN, Karl, Witold [GB/GB]; Langley Court, Beckenham, Kent BR3 3BS (GB). O'CONNOR, Kevin, Julian [GB/GB]; Cowl Cottage, Hill Top, Brenchley, Kent TN12 7NP (GB). HAWKE, Roy, Lee [US/US]; 105 Ludlow Court, Cary, NC 27513 (US). CHAPMAN, James, Mood [US/US]; 1111, Watermark Place, Columbia, SC 29210 (US).		<b>(74) Agent:</b> GARRETT, M.; The Wellcome Foundation Limited, Langley Court, Beckenham, Kent BR3 3BS (GB).  <b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.  <b>Published</b> <i>With international search report.</i>

**(54) Title:** ANTI-ATHEROSCLEROTIC ARYL COMPOUNDS**(57) Abstract**

The present invention is concerned with compounds of formula (I) wherein Ar is a mono- or bicyclic aromatic group optionally containing one or two heteroatoms independently selected from nitrogen, oxygen and sulphur, said group being optionally substituted by one or more atoms or groups independently selected from halogen, nitro, amino, -NRR<sup>1</sup> where R and R<sup>1</sup> are independently selected from hydrogen, C<sub>1-8</sub> alkyl and C<sub>1-8</sub> alkanoyl, cyano, carboxyalkoxy, alkoxycarbonylalkoxy, C<sub>1-8</sub> alkyl (including cycloalkyl and cycloalkylalkyl), C<sub>1-8</sub> alkoxy (including cycloalkoxy and cycloalkylalkoxy), C<sub>1-8</sub> thioalkyl, said alkyl, alkoxy and/or thioalkyl group(s) being optionally substituted by one or more halogen atoms, aryl, aryloxy, aralkyl and aralkyloxy, said aryl, aryloxy, aralkyl and/or aralkyloxy group(s) being optionally substituted by one or more atoms or groups independently selected from halogen, alkyl, alkoxy, alkanoyl, hydroxyalkyl, perfluoroalkyl, perfluoroalkoxy, carboxyalkoxy, alkoxycarbonylalkoxy, and C<sub>3-8</sub> polyether groups containing from one to three oxygen atoms; D is -CH<sub>2</sub>-, -NH-, or -O-; E is (a) or (b); G is hydrogen, C<sub>1-12</sub> straight, branched, or cyclic alkyl, or aralkyl, said aralkyl group being optionally substituted by one or more atoms or groups independently selected from halogen, amino, N-(C<sub>1-6</sub> alkyl)amino, N,N-di(C<sub>1-6</sub> alkyl)amino, C<sub>1-6</sub> alkyl and C<sub>1-6</sub> alkoxy, or a C<sub>3-8</sub> polyether group containing one to three oxygen atoms; J is a bond or C<sub>1-6</sub> straight or branched alkylene; n is an integer of from 0 to 10; R and R<sup>1</sup> are as hereinbefore defined; and K is -CH<sub>2</sub>OH, -CHO, -CONHCH<sub>2</sub>CONH<sub>2</sub>, -CONH(C<sub>1-6</sub> alkyl), -OC(C<sub>1-4</sub> alkyl)<sub>2</sub>OCO heteroaryl, -CO<sub>2</sub>R<sup>2</sup> where R<sup>2</sup> is hydrogen, C<sub>1-8</sub> alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or a C<sub>3-8</sub> polyether group containing from one to three oxygen atoms, or -CONHAr' where Ar' is phenyl optionally substituted by one or more atoms or groups selected from fluorine, nitro, -NRR<sup>1</sup> where R and R<sup>1</sup> are as hereinbefore defined, C<sub>1-6</sub> alkyl and C<sub>1-6</sub> alkoxy, said alkyl and/or alkoxy group(s) being optionally substituted at the terminal carbon by -CO<sub>2</sub>R<sup>3</sup> where R<sup>3</sup> is C<sub>1-6</sub> alkyl; and their physiologically functional derivatives, with processes for their preparation, with medicaments containing them and with their use as therapeutic agents, particularly in the prophylaxis and treatment of atherosclerosis.

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ANTI-ATHEROSCLEROTIC ARYL COMPOUNDS

The present invention is concerned with a novel genus of diaryl compounds, with processes for their preparation, with medicaments containing them and with their use as therapeutic agents, particularly in the prophylaxis and treatment of atherosclerosis.

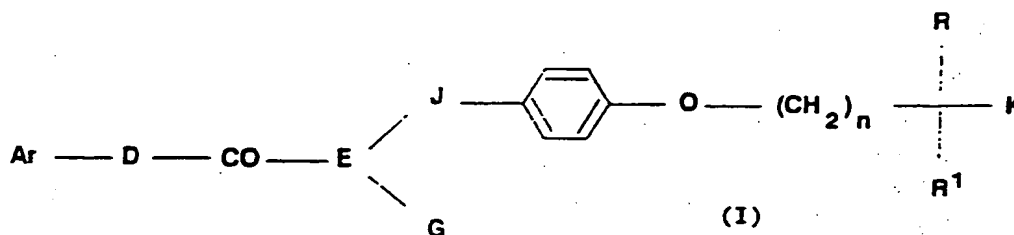
The enzyme acyl coenzyme A - cholesterol acyl transferase (ACAT) is known to be involved in the intestinal absorption of cholesterol and in the accumulation of cholesterol as cholesterol esters in the arterial wall. Thus compounds which inhibit ACAT have the potential of demonstrating both potent hypocholesterolaemic activity and a decrease in arterial cholesterol deposition.

A group of compounds known collectively as 'fibrates' which give rise to a modest decrease in LDL-cholesterol, a significant decrease in triglycerides and a marked elevation of HDL-cholesterol in the plasma have been found useful in the treatment of Type IIA, IIB, III, IV and V hyperlipidaemias. The increase in the level of HDL-cholesterol is particularly important since it facilitates the removal of free cholesterol from the arterial wall for return to the liver ('reverse cholesterol transport').

It follows that a drug combining the hypocholesterolaemic/anti-atherosclerotic properties of an ACAT inhibitor with hypolipidaemic/HDL-enhancing properties would be particularly useful in the prophylaxis and treatment of atherosclerosis, the enhanced HDL-cholesterol level induced giving rise to an increase in the capacity of the reverse cholesterol transport mechanism to remove the free cholesterol resulting from ACAT inhibition in the arterial wall. Such a drug would be especially beneficial to Type IIA and Type III patients having both high serum cholesterol and triglyceride levels who are at particular risk of contracting coronary heart disease.

On the basis of the foregoing, we have discovered a series of novel compounds having potential hypolipidaemic/hypocholesterolaemic activity.

According to the present invention, therefore, there is provided a compound of formula (I)



wherein

Ar is a mono- or bicyclic aromatic group optionally containing one or two heteroatoms independently selected from nitrogen, oxygen and sulphur, said group being optionally substituted by one or more atoms or groups independently selected from halogen, nitro, amino,  $-\text{NRR}^1$  where R and  $\text{R}^1$  are independently selected from hydrogen,  $\text{C}_{1-8}$  alkyl and  $\text{C}_{1-8}$  alkanoyl, cyano, carboxyalkoxy, alkoxycarbonylalkoxy,  $\text{C}_{1-8}$  alkyl (including cycloalkyl and cycloalkylalkyl),  $\text{C}_{1-8}$  alkoxy (including cycloalkoxy and cycloalkylalkoxy),  $\text{C}_{1-8}$  thioalkyl, said alkyl, alkoxy and/or thioalkyl group(s) being optionally substituted by one or more halogen atoms, aryl, aryloxy, aralkyl and aralkyloxy, said aryl, aryloxy, aralkyl and/or aralkyloxy group(s) being optionally substituted by one or more atoms or groups independently selected from halogen, alkyl, alkoxy, alkanoyl, hydroxyalkyl, perfluoroalkyl, perfluoroalkoxy, carboxyalkoxy, alkoxycarbonylalkoxy, and  $\text{C}_{3-8}$  polyether groups containing from one to three oxygen atoms;

D is  $-\text{CH}_2-$ ,  $-\text{NH}-$  or  $-\text{O}-$ ;

E is  $-N<$  or  $-CH<$ ;

G is hydrogen,  $C_{1-12}$  straight, branched, or cyclic alkyl, or aralkyl, said aralkyl group being optionally substituted by one or more atoms or groups independently selected from halogen, amino,  $N-(C_{1-6} \text{ alkyl})\text{amino}$ ,  $N,N\text{-di}(C_{1-6} \text{ alkyl})\text{amino}$ ,  $C_{1-6}$  alkyl and  $C_{1-6}$  alkoxy, or a  $C_{3-8}$  polyether group containing one to three oxygen atoms;

J is a bond or  $C_{1-6}$  straight or branched alkylene;

n is an integer of from 0 to 10;

R and  $R^1$  are as hereinbefore defined; and

K is  $-\text{CH}_2\text{OH}$ ,  $-\text{CHO}$ ,  $-\text{CONHCH}_2\text{CONH}_2$ ,  $-\text{CONH}(C_{1-6} \text{ alkyl})$ ,  $-\text{OC}(C_{1-4} \text{ alkyl})_2$ ,  $\text{OCOHeteroaryl}$ ,  $-\text{CO}_2R^2$  where  $R^2$  is hydrogen,  $C_{1-8}$  alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or a  $C_{3-8}$  polyether group containing from one to three oxygen atoms, or  $-\text{CONHAr}'$  where  $\text{Ar}'$  is phenyl optionally substituted by one or more atoms or groups selected from fluorine, nitro,  $-\text{NRR}^1$  where R and  $R^1$  are as hereinbefore defined,  $C_{1-6}$  alkyl and  $C_{1-6}$  alkoxy, said alkyl and/or alkoxy group(s) being optionally substituted at the terminal carbon by  $-\text{CO}_2R^3$  where  $R^3$  is  $C_{1-6}$  alkyl;

and salts and physiologically functional derivatives thereof.

Salts of compounds of formula (I) suitable for use in medicine are those which are physiologically acceptable. However, non-physiologically acceptable salts are within the scope of the present invention for use as intermediates in the preparation of the compounds of the invention and their physiologically acceptable salts and physiologically functional derivatives.

The "physiologically functional derivatives" referred to herein are compounds which are converted in vivo to a compound of formula (I) or one of its physiologically acceptable salts.

Preferred compounds of formula (I) having particularly good ACAT inhibiting/fibrate-like properties include those wherein

Ar is phenyl or naphthyl substituted by one or more atoms or groups independently selected from halogen, C<sub>1-8</sub> alkyl, C<sub>1-8</sub> alkoxy (including cycloalkylalkoxy), said alkyl and/or alkoxy group(s) being optionally substituted by one or more halogen atoms, C<sub>1-8</sub> thioalkyl, aryl, aryloxy and aralkoxy, said aralkoxy group being optionally substituted by alkyl, alkoyl, or hydroxyalkyl;

D is -NH- or -O-;

E is -N<;

G is C<sub>5-8</sub> straight or branched alkyl, (4-halophenyl)C<sub>1-3</sub> alkyl, or [4-di(C<sub>1-6</sub> alkyl)aminophenyl]C<sub>1-3</sub> alkyl;

J is C<sub>1-3</sub> alkylene;

n is an integer of from 0 to 4;

R and R<sup>1</sup> are respectively hydrogen and C<sub>1-4</sub> alkyl or are both C<sub>1-4</sub> alkyl; and

K is -CO<sub>2</sub>R<sup>2</sup> where R<sup>2</sup> is hydrogen or C<sub>1-4</sub> alkyl, or -CH<sub>2</sub>OH;

and physiologically acceptable salts and physiologically functional derivatives thereof.

Particularly preferred compounds of the invention are 2-(4-(2-[3-(2,4-dimethoxyphenyl)-1-heptylureido]ethyl)phenoxy)-2-methylpropionic acid,

2-(4-{2-[3-(2,4-difluorophenyl)-1-heptylureido]ethyl}phenoxy)-2-methylpropionic acid, 2-(4-[3-(2,4-dimethoxyphenyl)-1-heptylureidomethyl]phenoxy)-2-methyl-propionic acid, 2-(4-[1-heptyl-3-(2,4,6-trichlorophenyl)ureidomethyl]phenoxy)-2-methylpropionic acid, 2-(4-[1-(3,3-dimethylbutyl)-3-(2,4-dimethoxyphenyl)ureidomethyl]phenoxy)-2-methyl-propionic acid, 3-(2,4-dimethoxyphenyl)-1-heptyl-1-[4-(2-hydroxy-1-methylethoxy)benzyl]urea, 3-(2,4-dimethylphenyl)-1-heptyl-1-[4-(5-hydroxy-4,4-dimethylpentyloxy)benzyl]urea and their physiologically acceptable salts and physiologically functional derivatives.

According to further aspects of the invention, there are also provided:

- (a) compounds of formula (I) and physiologically acceptable salts and physiologically functional derivatives thereof for use as a therapeutic agent;
- (b) pharmaceutical formulations comprising a compound of formula (I) and/or one of its physiologically acceptable salts or physiologically functional derivatives and at least one pharmaceutical carrier;
- (c) the use of a compound of formula (I) or of a physiologically acceptable salt or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which an ACAT inhibitor and/or a fibrate is indicated;
- (d) a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which an ACAT inhibitor and/or a fibrate is indicated which comprises the administration of a therapeutically effective amount of a compound of formula (I) or of a physiologically acceptable salt or physiologically functional derivative thereof to said mammal; and

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(e) processes for the preparation of compounds of formula (I) and salts and physiologically functional derivatives thereof.

With regard to aspects (a), (c) and (d), the ability of compounds of formula (I) to inhibit ACAT activity renders them useful as hypocholesterolaemics and for reducing the steady state concentration of cholesterol and cholesterol ester in the arterial wall. Similarly, the fibrate-like activity of compounds of formula (I) renders them useful as hypolipidaemics and for increasing the capacity of the reverse cholesterol transport mechanism to remove free cholesterol from the arterial wall.

On the basis of their ability to regress established atherosclerotic plaque and retard the build-up of fresh lesions, compounds of formula (I) find application in both the prophylaxis and treatment of atherosclerosis.

In view of their hypocholesterolaemic/hypolipidaemic properties, compounds of formula (I) and their physiologically acceptable salts and physiologically functional derivatives may also find application in the prophylaxis and treatment of pancreatitis, in 'shifting' the oxygen affinity of human haemoglobin to improve myocardial function, for example, in the treatment of ischaemic tissue, and as uricosuric agents for reducing elevated plasma uric acid levels arising from, for example, hypertriglyceridaemia. The compounds of the invention also exhibit calcium antagonism in the ileum, stimulate hepatic fatty acid oxidation in the liver and have the potential to lower plasma triglycerides and elevate plasma HDL-cholesterol.

Hereinafter all references to "compound(s) of formula (I)" refer to compound(s) of formula (I) as defined above including their physiologically acceptable salts and physiologically functional derivatives.



The amount of a compound of formula (I) which is required to achieve the desired biological effect will, of course, depend on a number of factors, for example, the specific compound chosen, the use for which it is intended, the mode of administration and the clinical condition of the recipient. In general, the daily dose will be in the range 5mg to 1g, for example, 10mg per day. An intravenous dose may, for example, be in the range 100mg to 1g, which may conveniently be administered as an infusion of from 1mg to 100mg per minute. Infusion fluids suitable for this purpose may contain, for example, from 0.1mg to 10mg, typically 1mg, per millilitre. Unit doses may contain, for example, from 100mg to 1g of the active compound. Thus ampoules for injection may contain, for example, from 100mg to 500mg and orally administrable unit dose formulations, such as tablets or capsules, may contain, for example, from 100mg to 1g, typically 200mg. In the case of physiologically acceptable salts, the weights indicated above refer to the weight of the ion derived from the compound of formula (I).

For the prophylaxis or treatment of the conditions referred to above, the compounds of formula (I) may be used as the compound per se, but are preferably presented with an acceptable carrier in the form of a pharmaceutical formulation. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the formulation and must not be deleterious to the recipient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose formulation, for example, a tablet, which may contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances may also be present including other compounds of formula (I). The formulations of the invention may be prepared by any of the wellknown techniques of pharmacy consisting essentially of admixing the components.

The formulations include those suitable for oral, rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable route in any given case will depend on the nature

and severity of the condition being treated and on the nature of the particular compound of formula (I) which is being used.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of a compound of formula (I); as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and the carrier (which may constitute one or more accessory ingredients). In general, the formulations are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet may be prepared by compressing or moulding a powder or granules of the compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a compound of formula (I) in a flavoured base, usually sucrose and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

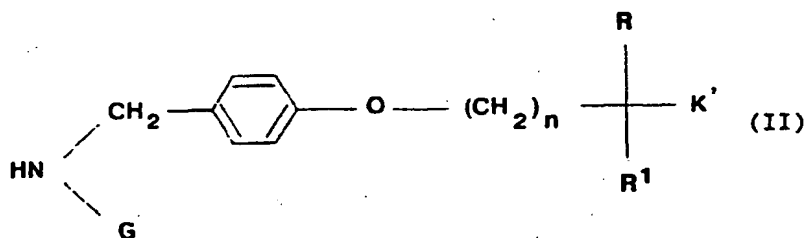
Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of formula (I), preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such

preparations may conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of the active compound.

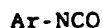
Formulations suitable for rectal administration are preferably presented as unit-dose suppositories. These may be prepared by admixing a compound of formula (I) with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

Compounds of formula (I) may be prepared by conventional means well known to a skilled person. Thus compounds of formula (I) wherein D is -NH- and E is -N< may be prepared by reacting a compound of formula (II)



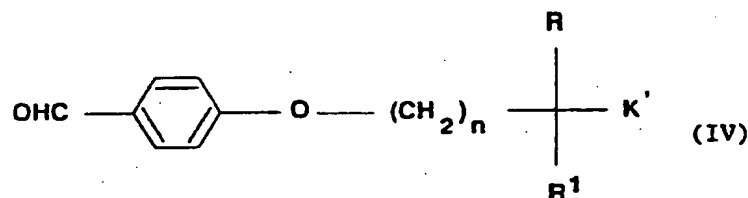
wherein n, G, J, R and R<sup>1</sup> are as hereinbefore defined and K' is as hereinbefore defined for K or is a suitably protected form thereof, with a compound of formula (III)



(III)

wherein Ar is as hereinbefore defined, typically in an aprotic polar solvent, for example, dichloromethane, and, if necessary, deprotecting the product.

Compounds of formula (II) wherein J is  $-\text{CH}_2-$  may be prepared by reacting a compound of formula (IV)

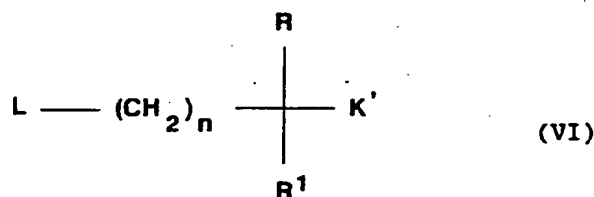


wherein n, R,  $\text{R}^1$  and  $\text{K}'$  are as hereinbefore defined, with a compound of formula (V)



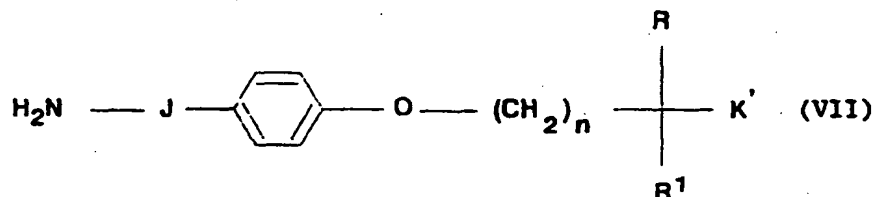
wherein G is as hereinbefore defined, typically by refluxing in a polar solvent, for example, ethanol, and reducing the resulting imine by, for example, hydrogenation over Pd/C.

Compounds of formula (IV) may be prepared by reacting commercially available 4-hydroxybenzaldehyde with a compound of formula (VI)



wherein n,  $\text{K}'$ , R and  $\text{R}^1$  are as hereinbefore defined and L is a suitable leaving group, for example, bromo, typically by refluxing in a polar solvent, for example, ethanol, in the presence of potassium carbonate.

Compounds of formula (II) wherein J is C<sub>2-6</sub> straight or branched alkylene may be prepared by reacting a compound of formula (VII)

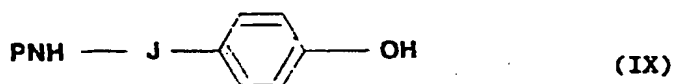


wherein n, J, K', R and R<sup>1</sup> are as hereinbefore defined, with a compound of formula (VIII)



wherein G' is as hereinbefore defined for G less a terminal methylene group, typically by mixing the two compounds together and reducing the resulting imine by, for example, hydrogenation over Pd/C.

Compounds of formula (VII) may be prepared by reacting a compound of formula (IX)



wherein J is as hereinbefore defined and P is a suitable protecting group, for example, benzyloxycarbonyl, with a compound of formula (VI) as hereinbefore defined, typically by refluxing in a polar solvent, for example, ethanol, in the presence of a base, for example, KOH, and deprotecting the product by, for example, in the case where P is benzyloxycarbonyl, hydrogenation over Pd/C.

Compounds of formula (IX) may be prepared from the corresponding amine (X) by treatment with a compound of formula (XI)

L-P

(XI).

wherein L is a suitable leaving group, for example, chloro, and P is a suitable amino protecting group, for example, benzyloxycarbonyl.

Compounds of formula (III), (V), (VI), (VIII), (X) and (XI) are commercially available or may be prepared by methods well known to a skilled person or obtainable from the chemical literature.

Optional conversion of a compound of formula (I) to a corresponding salt may be effected by reaction with the appropriate acid or base. Optional conversion to a physiologically functional derivative may be carried out by methods well known to a skilled person or obtainable from the chemical literature.

For a better understanding of the invention, the following Examples are given by way of illustration.

#### Synthetic Example 1

##### Preparation of 2-(4-([3-(2,4-dimethoxyphenyl)-1-heptylureido]methyl)-phenoxy)-2-methylpropionic acid

##### (a) Ethyl 2-(4-formylphenoxy)-2-methylpropanoate

4-Hydroxybenzaldehyde (24.4g, Aldrich) was dissolved in absolute ethanol (470ml) and anhy.  $K_2CO_3$  (27.6g) and ethyl 2-bromoiso-butyrate (39.0g, Aldrich) added. The resulting mixture was refluxed overnight, allowed to cool and the solvent removed in vacuo. The residue was suspended in water (300ml) and extracted with  $CH_2Cl_2$ . The combined organic layers were washed with 1.0N aq. NaOH and water, then dried over  $MgSO_4$ . Removal of the solvent in vacuo and vacuum distillation of the residue gave the desired product (18.8g, bp 110-118°C/0.1mm Hg).

(b) Ethyl-N-n-heptyl-2-(4-aminomethylphenoxy)-2-methylpropanoate

The product from step (a) (4.72g) was dissolved in absolute ethanol (140ml) and n-heptylamine (2.3g, Aldrich) added. The resulting solution was refluxed for one hour, 10% Pd/C added and the suspension placed on a Paar hydrogenation apparatus - uptake of hydrogen ceased after approximately ten minutes. The suspension was filtered and the filtrate evaporated in vacuo to give the desired product as a clear oil (6.2g).

(c) N-(2,4-Dimethoxyphenyl)-N'-heptyl-N'-[p-[2-(carbethoxy)isopropoxy]phenyl]methylurea

The product from step (b) (3.49g) was dissolved in  $\text{CH}_2\text{Cl}_2$  (100ml) and 2,4-dimethoxyphenylisocyanate (1.9g, Aldrich) added. The resulting solution was stirred for 8 hours and then evaporated in vacuo. The residue was flash chromatographed through a silica column using hexanes/ $\text{CH}_2\text{Cl}_2$ /EtOAc (38:31:31) as eluant to give the desired product as a colourless oil (4.9g).

(d) N-(2,4-Dimethoxyphenyl)-N'-heptyl-N'-[p-[2-(carboxy)isopropoxy]phenyl]methylurea

The product from step (c) (4.85g) was dissolved in ethanol (25ml) and 1.0N aq. NaOH (15ml) added. The resulting solution was heated to effect dissolution and then refluxed for 4 hours. After cooling,  $\text{CH}_2\text{Cl}_2$  (100ml) and 1.0N aq. HCl (60ml) were added. The organic layer was separated and the aqueous layer extracted with additional  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with water, dried over  $\text{MgSO}_4$  and evaporated in vacuo to leave a pale yellow viscous oil which upon crystallization from hexanes/ether gave the desired product as a colourless solid (2.1g), mp 80-81°C.

$^1\text{H}$  NMR (500MHz,  $\delta$ ,  $\text{CDCl}_3$ ): 6.33-8.04 (m, 8H, aromatic, NH), 4.44 (s, 2H,  $\text{CH}_2$ -phenyl, 3.61/3.69 (2 x s, 6H, 2,4-( $\text{OCH}_3$ ) $_2$ ), 3.26 (t, 2H,  $\text{N-CH}_2$ -( $\text{CH}_2$ ) $_5\text{CH}_3$ ) and 0.65-1.80 (m, 19H, ( $\text{CH}_2$ ) $_5\text{CH}_3$ , ( $\text{CH}_3$ ) $_2\text{C}$ )

FAB MS:  $(\text{M}-1)^+ = 485$

Elemental analysis ( $\text{C}_{27}\text{H}_{38}\text{N}_2\text{O}_6$ ): C 66.57% (66.64%), H 7.90% (7.87%), N 5.72% (5.76%)

### Synthetic Example 2

#### Preparation of 2-(4-(2-[3-(2,4-dimethoxyphenyl)-1-heptylureido]ethyl)-phenoxy)-2-methylpropionic acid

##### (a) Carbobenzyloxytyramine

Sodium bicarbonate (12.6g) was dissolved in distilled water (250ml) and tyramine (20.6g) added. The resulting suspension was heated to boiling to dissolve the tyramine, then cooled to room temperature. Benzyl chloroformate (25.6g) was added while stirring and with occasional vigorous shaking. After stirring and shaking for an additional 1.5 hours, the precipitate was filtered off and washed with distilled water. The solid was dissolved in ether (250ml) and washed with distilled water. The organic layer was dried over  $\text{MgSO}_4$  and evaporated in vacuo to give a residue which solidified upon cooling. Recrystallization from ether/hexane gave the desired product as colourless crystals, m.p. 96-98°C.

##### (b) Ethyl 2-[4-(2-carbobenzyloxyamino)ethyl]phenoxy-2-methylpropionate

The product from step (a) (42.8g) and KOH (6.2g) were dissolved with warming in absolute ethanol (600ml). Ethyl 2-bromoisobutyrate (21.7g) was added and the resulting solution refluxed for



5.5 hours. Additional KOH (4.0g) and ethyl 2-bromoisobutyrate (11.3g) were then added and refluxing continued for 16.5 hours. After cooling, the precipitated KBr was removed by filtration and the filtrate evaporated in vacuo to give a light brown oil. The oil was dissolved in  $\text{CH}_2\text{Cl}_2$  (500ml), washed with 1.0N aqu. NaOH, satd. aqu. NaCl, 1.0N aqu. HCl and satd. aqu. NaCl, dried over  $\text{MgSO}_4$  and the solution evaporated in vacuo. The residue was flash chromatographed through a silica column using hexanes/ $\text{CH}_2\text{Cl}_2$ /EtOAc (50:25:25) as eluant to give the desired product as a colourless oil (23.5g).

(c) Ethyl 2-[4-(2-aminoethyl)phenoxy]-2-methylpropionate

The product from step (b) (2.7g) was dissolved in ethanol (100ml) and 10% Pd/C (0.3g) added. Paar hydrogenation for 45 minutes resulted in a drop in bottle pressure from 48.5 to 41.0 psi. The Pd/C was removed by filtration and the filtrate evaporated in vacuo to give the desired product as a colourless oil (1.5g).

(d) Ethyl 2-[4-(heptylaminoethyl)phenoxy]-2-methylpropionate

The product from step (c) (1.5g) and heptaldehyde (0.7g) were mixed together in a observably exothermic reaction and the product dissolved in absolute ethanol (100ml). Paar hydrogenation for 1.0 hour resulted in a drop in bottle pressure from 49.0 to 42.7 psi. The Pd/C was removed by filtration and the filtrate evaporated in vacuo to give the desired product as a colourless oil (2.1g).

(e) Ethyl 2-(4-[2-[3-(2,4-dimethoxyphenyl)-1-heptylureido]ethyl]-phenoxy)-2-methylpropionate

The product from step (d) (2.1g) and 2,4-dimethoxyphenylisocyanate (1.1g, Aldrich) were dissolved in  $\text{CH}_2\text{Cl}_2$  (50ml). The resulting solution was stirred at room temperature for 17 hours

and then evaporated in vacuo. The residue was flash chromatographed through a silica column using hexanes/ $\text{CH}_2\text{Cl}_2$ /EtOAc (50:25:25) as eluant to give the desired product as a very light brown oil (2.0g).

(f) 2-(4-(2-[3-(2,4-Dimethoxyphenyl)-1-heptylureido]ethyl)phenoxy)-2-methylpropionic acid

The product from step (e) (2.0g) was dissolved in absolute ethanol (50ml) and 1.0N aq. NaOH (30ml) added. The resulting solution was refluxed for 0.5 hour, cooled to room temperature, acidified with 2.0N aq. HCl (100ml) and extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with water and satd. aq. NaCl, dried over  $\text{MgSO}_4$  and evaporated in vacuo to give a viscous yellow oil. Repeated recrystallization from ether/hexanes gave the desired product as colourless crystals (1.5g), mp 95-96°C.

$^1\text{H}$  NMR (500MHz,  $\delta$ ,  $\text{CDCl}_3$ ) 6.44-7.99 (m, 7H, aromatic), 3.82 (s, 3H,  $\text{OCH}_3$ ), 3.76 (s, 3H,  $\text{OCH}_3$ ), 3.45 (t, 2H,  $\text{CH}_2$ ), 3.18 (s, 3H,  $\text{CH}_2$ ), 2.84 (s, 3H,  $\text{CH}_2$ ), 1.55-1.58 (m, 8H,  $\text{C}(\text{CH}_3)_2$ ,  $\text{CH}_2$ ), 1.26-1.30 (m, 8H,  $(\text{CH}_2)_4$ ) and 0.86 (t, 3H,  $(\text{CH}_2)_6\text{CH}_3$ )

FAB MS:  $(\text{M}-1)^+ = 499$

Elemental analysis ( $\text{C}_{28}\text{H}_{40}\text{N}_2\text{O}_6$ ): C 67.28% (67.17%), H 8.10% (8.05%), N 5.57% (5.60%)

Synthetic Example 3

Preparation of 2-(4-(2-[3-(2,4-difluorophenyl)-1-heptylureido]ethyl)phenoxy)-2-methylpropionic acid

(a) Ethyl 2-[4-(heptylaminoethyl)phenoxy]-2-methylpropionate

As for steps (a) to (d) of Synthetic Example 2.

(b) Ethyl 2-(4-(2-(3-(2,4-difluorophenyl)-1-heptylureido)ethyl)-phenoxy)-2-methylpropionate

The product from step (d) (3.3g) was dissolved in  $\text{CH}_2\text{Cl}_2$  (100ml) and 2,4-difluorophenylisocyanate (1.6g, Aldrich) added. The resulting solution was stirred overnight at room temperature and then evaporated in vacuo. The residue was flash chromatographed through a silica column using toluene/hexanes/ $\text{CH}_2\text{Cl}_2$ /EtOAc (50:30:10:10) as eluant to give the desired product as a colourless oil (4.8g).

(c) 2-(4-(2-(3-(2,4-Difluorophenyl)-1-heptylureido)ethyl)phenoxy)-2-methylpropionic acid

The product from step (e) (2.4g) was dissolved in absolute ethanol (25ml) and 1.0N aq. NaOH (10ml) added. The resulting solution was stirred at room temperature for 3.7 hours, acidified with 1.0M aq. HCl (100ml) and extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with brine (50ml), dried over  $\text{MgSO}_4$  and evaporated in vacuo to give a colourless oil which was flash chromatographed through a silica column using hexanes/ $\text{CH}_2\text{Cl}_2$ /EtOAc (50:25:25) as eluant to give the desired product as a very pale yellow viscous oil (1.4g).

$^1\text{H}$  NMR (500MHz,  $\delta$ ,  $\text{CDCl}_3$ ): 6.77-7.99 (m, 6H, aromatic), 6.27 (s, 1H, NH), 4.10 (q, 4H,  $\text{OCH}_2$ ), 3.48 (t, 2H,  $\text{CH}_2$ ), 3.19 (t, 2H,  $\text{CH}_2$ ), 2.84 (t, 2H,  $\text{CH}_2$ ), 1.59 (m, 2H,  $\text{CH}_2$ ), 1.53 (s, 6H,  $(\text{CH}_3)_2\text{C}$ ), 1.22-1.28 (m, 10H,  $(\text{CH}_2)_5$ ) and 0.86 (t, 3H,  $(\text{CH}_2)_6\text{CH}_3$ )

FAB MS:  $(\text{M}-1)^+ = 475$

Elemental analysis ( $\text{C}_{26}\text{H}_{34}\text{F}_2\text{N}_2\text{O}_4$ ): C 65.65% (65.53%), H 7.24% (7.19%), N 5.86% (5.88%).

Synthetic Examples 4-98

The following compounds of formula (I) were prepared by methods analogous to those of Synthetic Examples 1 to 3. All compounds have  $^1\text{H}$  NMRs and elemental analyses consistent with the proposed structures.

- 4) Ethyl 2-(4-[3-(4-chlorophenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionate, mp 46-48°C;
- 5) 2-(4-[3-(4-Chlorophenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionic acid, mp 120-122°C;
- 6) Ethyl 2-[N'-(4-chloro-2-trifluoromethylphenyl)-N-heptylureido-methylphenoxy]-2-methylpropionate, colourless oil;
- 7) Ethyl 2-(4-([1-heptyl-3-(2,4,6-trichlorophenyl)ureido]methyl)-phenoxy)-2-methylpropionate, pale yellow liquid;
- 8) 2-(4-([1-Heptyl-3-(2,4,6-trichlorophenyl)ureido]methyl)phenoxy)-2-methylpropionic acid, mp 52-54°C;
- 9) Ethyl 2-[3-(2,4-difluoro-6-methoxyphenyl)-1-heptylureidomethyl-phenoxy]-2-methylpropionate, colourless oil;
- 10) 1-(2,4-Difluoro-6-methoxyphenyl)-3-[4-(2-hydroxy-1,1-dimethylethoxy)benzyl]urea, colourless oil;
- 11) 2-(4-(3-(2-Ethoxyphenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropanol, pale tan oil;
- 12) 2-(4-([3-(2,4-Dimethoxyphenyl)-1-heptylureido]methyl)phenoxy)-propionic acid, mp 98-99°C;

- 13) Ethyl 5-(4-([3-(2,4-dimethoxyphenyl)-1-heptylureido]methyl)phenoxy)-2,2-dimethylvalerate, colourless oil;
- 14) 2-[4-([1-[2-(4-Chlorophenyl)ethyl]-3-(2,4-dimethoxyphenyl)ureido]methyl)phenoxy]-2-methylpropionic acid, mp 118.5-120°C;
- 15) (4-([3-(2,4-Dimethoxyphenyl)-1-octylureido]methyl)phenoxy)-2-methylpropionic acid, mp 62-64°C;
- 16) Ethyl (4-([3-(2,4-dimethoxyphenyl)-1-pentylureido]methyl)phenoxy)-2-methylpropionate, yellow oil;
- 17) 2-(4-([3-(2,4-Dimethoxyphenyl)-1-pentylureido]methyl)phenoxy)-2-methylpropionic acid, mp 119-120°C;
- 18) 2-(4-([1-(3,3-Dimethylbutyl)-3-(2,4-dimethoxyphenyl)ureido]methyl)phenoxy)-2-methylpropionic acid, mp 149-150°C;
- 19) 1-Heptyl-1-[4-(2-hydroxy-1,1-dimethylethoxy)benzyl]-3-(2,4,6-trimethoxyphenyl)urea, mp 109-110°C;
- 20) 3-(2,4-Dimethoxyphenyl)-1-heptyl-1-[4-(2-hydroxy-1-methylethoxy)benzyl]urea, colourless oil;
- 21) Ethyl 2-[4-(N'-2-biphenyl-N-heptylureidomethyl)phenoxy]-2-methylpropionate, mp 61-62°C;
- 22) 2-[4-[3-(2-Biphenyl)-1-heptylureidomethyl]phenoxy]-2-methylpropionic acid 0.75 potassium salt, no mp (amorphous solid);
- 23) Ethyl 2-[4-[1-heptyl-3-(2-phenoxyphenyl)ureidomethyl]phenoxy]-2-methylpropionate, pale tan gum;
- 24) 3-(2,4-Dimethylphenyl)-1-heptyl-1-[4-[(5-hydroxy-4,4-dimethylpentyl)oxy]benzyl]urea, colourless oil;

- 25) Ethyl 2-(4-[3-(2-ethoxy-4,6-difluorophenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionate, colourless oil;
- 26) Ethyl 2-(4-[3-(4-chloro-2-ethoxyphenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionate, colourless oil;
- 27) Ethyl 2-(4-([3-(2,4-dimethoxyphenyl)-1-heptylureido]methyl)phenoxy)-2-methylpropionate, colourless oil;
- 28) Ethyl 2-(4-([3-(5-chloro-2,4-dimethoxyphenyl)-1-heptylureido]methyl)phenoxy)-2-methylpropionate, yellow oil;
- 29) Ethyl 2-(4-[3-(2-ethoxy-1-naphthyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionate, mp 89-91°C;
- 30) Ethyl 2-[N'-(2,5-di-*t*-butylphenyl)-N-heptylureidomethylphenoxy]-2-methylpropionate, mp 82.5-84.5°C;
- 31) 2-(4-[3-(2-Biphenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropanol, colourless oil;
- 32) Ethyl 2-(4-[3-(4-fluorenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionate, mp 78-79°C;
- 33) Ethyl 2-([3-(2-fluorophenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionate, colourless oil;
- 34) Ethyl 2-(4-[3-(2,6-difluorophenyl)-1-heptylureidomethyl]phenoxy)-isobutyrate, colourless oil;
- 35) Ethyl 2-(4-[3-(2,4-difluorophenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionate, colourless oil;
- 36) Ethyl 2-[4-(2,4-difluoro-N-heptylphenylacetamidomethyl)phenoxy]-2-methylpropionate, very pale yellow oil;

- 37) Ethyl 2-(4-[1-t-butyl-3-(2,4-difluorophenyl)ureidomethyl]phenoxy)-2-methylpropionate, mp 80-82°C;
- 38) Ethyl 5-(4-[3-(2,4-difluorophenyl)-1-heptylureidomethyl]phenoxy)-valerate, colourless oil;
- 39) Ethyl 2-(4-(3-[2-(4-t-butylbenzyloxy)-4,6-difluorophenyl]-1-heptylureidomethyl)phenoxy)-2-methylpropionate, colourless oil;
- 40) Ethyl 2-(N'-[2-(4-t-butylbenzyloxy)phenyl]-N-heptylureidomethyl)-phenoxy-2-methylpropionate, colourless oil;
- 41) Ethyl 2-(4-(N'-[2-(4-t-butylbenzyloxy)-4-chlorophenyl]-N-heptylureidomethyl)phenoxy)-2-methylpropionate, mp 76-78°C;
- 42) Ethyl 2-(4-([(4-chlorophenoxy)carbonyl]heptylaminomethyl)phenoxy)-2-methylpropionate, no mp (amorphous solid);
- 43) Ethyl 2-(4-[3-(4-chlorophenyl)-1-dodecylureidomethyl]phenoxy)-2-methylpropionate, yellow oil;
- 44) Ethyl 2-(4-([(4-chlorophenoxy)carbonyl]dodecylaminomethyl)phenoxy)-2-methylpropionate, colourless viscous oil;
- 45) Ethyl 5-(4-[3-(4-chlorophenyl)-1-heptylureidomethyl]phenoxy)valerate, colourless oil;
- 46) 1-(4-Chloro-2-trifluoromethylphenyl)-3-heptyl-3-[4-(2-hydroxy-2,2-dimethylethoxy)benzyl]urea, colourless oil;
- 47) 2-(4-[3-(2,4-Dichlorophenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionic acid, mp 73-74.5°C;
- 48) Ethyl 2-(4-[3-(3,4-dichlorophenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionate, no mp (colourless wax);

- 49) Ethyl 2-(4-[1-dodecyl-3-(2,4,6-trichlorophenyl)ureidomethyl]phenoxy)-2-methylpropionate, colourless oil;
- 50) Ethyl 2-(4-[3-(4-chloro-2-nitrophenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionate, yellow oil;
- 51) Ethyl 2-(4-[1-heptyl-3-(2-methoxyphenyl)ureidomethyl]phenoxy)-2-methylpropionate, yellow oil;
- 52) Ethyl (4-[3-(4-methoxyphenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionate, no mp (colourless wax);
- 53) Ethyl 2-(4-[1-heptyl-3-(2-trifluoromethoxyphenyl)ureidomethyl]phenoxy)-2-methylpropionate, colourless oil;
- 54) Ethyl 2-(4-[3-[2-fluoro-6-(2,2,2-trifluoroethoxy)phenyl]-1-heptylureidomethyl]phenoxy)-2-methylpropionate, pale tan oil;
- 55) 2-(4-[3-(4-Chloro-2-methoxyphenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionic acid, mp 121-122°C;
- 56) Ethyl 2-(4-[1-heptyl-3-(2-methylthiophenyl)ureidomethyl]phenoxy)-2-methylpropionate, colourless oil;
- 57) Ethyl 2-(4-[N'-(2-Ethoxyphenyl)-N-heptylureidomethyl]phenoxy)-2-methylpropionate, colourless oil;
- 58) Ethyl 2-(4-[3-(2,4-dichloro-6-ethoxyphenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionate, colourless oil;
- 59) 2-Ethoxyphenyl N-[4-(1-ethoxycarbonyl-1-methylethoxy)benzyl]-N-heptylcarbamate, colourless oil;
- 60) Ethyl 2-(4-[1-heptyl-3-(2-propoxyphenyl)ureidomethyl]phenoxy)-2-methylpropionate, colourless oil;



- 61) Ethyl 2-(4-[3-(2,6-dimethoxyphenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionate, colourless oil;
- 62) Ethyl 2-[4-(N-heptyl-2,4-dimethoxyphenylacetamidomethyl)phenoxy]-2-methylpropionate, pale tan oil;
- 63) 2-(4-[3-(2,4-Dimethoxyphenyl)-1-heptylureidomethyl]phenoxy)butyric acid, pale yellow oil;
- 64) 3-(2,4-Dimethoxyphenyl)-1-heptyl-1-[4-(1-hydroxymethylpropoxy)-benzyl]urea, tan oil;
- 65) 5-(4-[3-(2,4-Dimethoxyphenyl)-1-heptylureidomethyl]phenoxy)-2,2-dimethylvaleric acid, tan oil;
- 66) 2-(4-[1-Heptyl-3-(2,4,6-trimethoxyphenyl)ureidomethyl]phenoxy)-2-methylpropionic acid, mp 140-142°C;
- 67) Ethyl 2-(4-[1-[2-(4-chlorophenyl)ethyl]-3-(2,4-dimethoxyphenyl)-ureidomethyl]phenoxy)-2-methylpropionate, mp 89.5-91°C;
- 68) 2-(4-[3-(2,4-Dimethoxyphenyl)-1-nonylureidomethyl]phenoxy)-2-methylpropionic acid, mp 55-57°C;
- 69) Ethyl 2-(4-[3-(2,4-dimethoxyphenyl)-1-propylureidomethyl]phenoxy)-2-methylpropionate, mp 69-71°C;
- 70) 2-(4-[3-(2,4-Dimethoxyphenyl)-1-propylureidomethyl]phenoxy)-2-methylpropionic acid, mp 96-98°C;
- 71) Ethyl 2-(4-[1-t-butyl-3-(2,4-dimethoxyphenyl)ureidomethyl]phenoxy)-2-methylpropionate, mp 80-81°C;
- 72) Ethyl 2-(4-[3-(2,4-difluoro-6-methoxyphenyl)-1-(1,1-dimethyloctyl)ureidomethyl]phenoxy)-2-methylpropionate, mp 57-59°C;

- 73) Ethyl 2-(4-[3-(2,4-dimethoxyphenyl)-1-(1,1-dimethoxyhexyl)ureidomethyl]phenoxy)-2-methylpropionate, pale tan oil;
- 74) Ethyl 2-(4-[3-chloro-2-thienyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionate, yellow-tan oil;
- 75) 3-(2,4-Dimethoxyphenyl)-1-heptyl-1-(2-[4-(2-hydroxy-1,1-dimethylethoxy)phenyl]ethyl)urea, tan oil;
- 76) 2-(4-(2-[1-Heptyl-3-(2,4,6-trimethoxyphenyl)ureido]ethyl)phenoxy)-2-methylpropionic acid, mp 100-102°C;
- 77) 2-(4-(2-[1-Heptyl-3-(2,4,6-trimethylphenyl)ureido]ethyl)phenoxy)-2-methylpropionic acid, mp 53-103°C (glass);
- 78) 2-(4-(2-[1-Heptyl-3-(2,4,6-trichlorophenyl)ureido]ethyl)phenoxy)-2-methylpropionic acid, mp 47-55°C;
- 79) 2-(4-(2-[3-(2,6-Diisopropylphenyl)-1-heptylureido]ethyl)phenoxy)-2-methylpropionic acid, mp 56-57°C;
- 80) 1-(2-[4-(2-Hydroxy-1,1-dimethylethoxy)phenyl]ethyl)-3-(2,4-dimethoxyphenyl)-1-(6,6-dimethylheptyl)urea, colourless oil;
- 81) 2-(4-(2-[3-(2,4-Dimethoxyphenyl)-1-(3,3-dimethylbutyl)ureido]ethyl)phenoxy)-2-methylpropionic acid, 145-147°C;
- 82) 5-(4-(2-[3-(2,4-Dimethoxyphenyl)-1-heptylureido]ethyl)phenoxy)-2,2-dimethylvaleric acid, tan oil;
- 83) 2-(4-(3-[3-(2,4-Dimethoxyphenyl)-1-heptylureido]propyl)phenoxy)-2-methylpropionic acid, yellow oil;
- 84) Ethyl 2-(4-[1-heptyl-3-(2-tolyl)ureidomethyl]phenoxy)-2-methylpropanoate, colourless oil;

- 85) Ethyl 2-(4-[N'-(2,6-dimethylphenyl)-N-heptylureidomethyl]phenoxy)-2-methylpropionate, mp 68-70°C;
- 86) Ethyl 2-(4-[N'-(4-bromo-2,6-dimethylphenyl)-N-heptylureidomethyl]phenoxy)-2-methylpropionate, mp 72-74°C;
- 87) Ethyl 2-(4-[1-heptyl-3-(2-isopropylphenyl)ureidomethyl]phenoxy)-2-methylpropionate, mp 38-39°C;
- 88) Ethyl 2-(4-[1-heptyl-3-(2-isopropyl-6-methylphenyl)ureidomethyl]phenoxy)-2-methylpropionate, mp 88-90°C;
- 89) Ethyl 2-(4-[3-(2,6-diisopropylphenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionate, mp 135-136°C;
- 90) Ethyl 2-(4-[1-heptyl-3-(1-methoxy-2-naphthyl)ureidomethyl]phenoxy)-2-methylpropionate, pale green oil;
- 91) Ethyl 2-(4-(1-[2-fluoro-6-(4-pivaloylbenzyloxy)]-3-heptylureidomethyl]phenoxy)-2-methylpropionate, colourless oil;
- 92) Ethyl 2-(4-(3-[2-(4-*t*-butylbenzyloxy)-4-methoxyphenyl]-1-heptylureidomethyl]phenoxy)-2-methylpropionate, pale tan oil;
- 93) Ethyl 2-[4-(3-(2-fluoro-6-[4-(1-hydroxy-2,2-dimethylpropyl)benzyloxy]phenyl)-1-heptylureidomethyl]phenoxy]-2-methylpropionate, almost colourless oil;
- 94) Ethyl 2-(4-(3-[2,4-dichloro-6-(4-pivaloylbenzyloxy)phenyl]-1-heptylureidomethyl]phenoxy)-2-methylpropionate, pale yellow gum;
- 95) 3-(2,4-Dimethoxyphenyl)-1-heptyl-1-[4-(2-hydroxy-1,1-dimethylethoxy)benzyl]urea, yellow oil;

- 96) 2-(4-[3-(2,4-Difluorophenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionic acid, no mp (amorphous solid);
- 97) Ethyl 2-(4-[3-(2-cyclohexylmethoxy-4-methoxyphenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionate, pale tan oil; and
- 98) 2-(4-[2-[3-(2,4-Dimethoxyphenyl)ureido]ethyl]phenoxy)-2-methylpropionic acid, mp 159-160°C.

#### Pharmaceutical Formulation Examples

In the following Examples, the "active ingredient" is any compound of formula (I) as hereinbefore defined, preferably one of the compounds of Synthetic Examples 1 to 98.

##### Tablet

	<u>Per tablet</u>
Active Ingredient	5.0 mg
Lactose	82.0 mg
Starch	10.0 mg
Povidone	2.0 mg
Magnesium Stearate	1.0 mg

Mix together the active ingredient, lactose and starch. Granulate the powders using a solution of povidone in purified water. Dry the granules, add the magnesium stearate and compress to produce 100mg tablets.

##### Controlled release tablet

	<u>Per tablet</u>
Active ingredient	500 mg
Hydroxypropylmethylcellulose (Methocel K4M Premium)	112 mg
Lactose B.P.	53 mg
Povidone B.P.C.	28 mg
Magnesium Stearate	<u>7</u> mg
	700 mg

The formulation may be prepared by wet granulation of the first three ingredients with the solution of povidone, followed by addition of the magnesium stearate and compression.

#### Capsule

	<u>Per capsule</u>
Active ingredient	250 mg
Lactose B.P.	143 mg
Sodium Starch Glycollate	25 mg
Magnesium Stearate	<u>2</u> mg
	420 mg

Capsules may be prepared by admixing the ingredients of the formulation and filling two-part hard gelatin capsules with the resulting mixture.

#### Controlled release capsule

	<u>Per capsule</u>
Active ingredient	250 mg
Microcrystalline Cellulose	125 mg
Lactose B.P.	125 mg
Ethyl Cellulose	<u>13</u> mg
	513 mg

The controlled-release capsule formulation may be prepared by extruding a mixture of the first three ingredients, then spheronising and drying the extrudate. The dried pellets are coated with the ethyl cellulose as a controlled-release membrane and filled into two-part hard gelatin capsules.

#### Powder capsule for inhalation

	<u>Per capsule</u>
Active Ingredient (0.5-7.0 $\mu$ m powder)	4.0 mg
Lactose (30-90 $\mu$ m powder)	<u>46.0</u> mg
	50.0 mg

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The powders were mixed until homogeneous and filled into suitably sized hard gelatin capsules (50mg per capsule).

Injectable solution

Active ingredient	101 mg
Glycerol formal	3.5 ml

The active ingredient was dissolved in the glycerol formal by shaking the mixture for 2-3 minutes. The resulting solution was distributed into ampoules under aseptic conditions.

Oral solution A

Active ingredient	414 mg
Glycerol formal	7.0 ml

The active ingredient was dissolved in the glycerol formal by shaking the mixture for 2-3 minutes. The resulting solution was distributed into ampoules under aseptic conditions.

Oral solution B

Active ingredient	179 mg
Labrafil M1944 CS (Gattefosse)	7.0 ml

The active ingredient was dissolved in the Labrafil M1944 CS by stirring the mixture at 40-45°C for 5-10 minutes. The resulting solution was distributed into ampoules under aseptic conditions.

Intramuscular injection formulation

Active ingredient	0.20 g
Benzyl Alcohol	0.10 g
Glycofurool 75	1.45 g
Water for Injection	q.s. to 3.00 ml

The active ingredient is dissolved in the glycofurol. The benzyl alcohol is added and dissolved, then water added to 3ml. The solution is filtered through a sterile micropore filter and sealed in sterile 3ml glass vials.

#### Inhalation aerosol

Active Ingredient (0.5-7.0 $\mu$ m powder)	200 mg
Sorbitan Trioleate	100 mg
Saccharin Sodium (0.5-7.0 $\mu$ m powder)	5 mg
Methanol	2 mg
Trichlorofluoromethane	4.2 g
Dichlorodifluoromethane	to 10.0 ml

The sorbitan trioleate and menthol are dissolved in the trichlorofluoromethane. The saccharin sodium and active ingredient are dispersed in the mixture which is then transferred to a suitable aerosol canister and the dichlorofluoromethane injected through the valve system. This composition provides 2mg of active ingredient in each 100 $\mu$ l dose.

#### Syrup formulation

Active ingredient	0.25 g
Sorbitol Solution	1.50 g
Glycerol	1.00 g
Sodium Benzoate	0.0050 g
Flavour	0.0125 ml
Purified Water	q.s. to 5.0 ml

The sodium benzoate is dissolved in a portion of the purified water and the sorbitol solution added. The active ingredient is added and dissolved. The resulting solution is mixed with the glycerol and then made up to the required volume with the purified water.

Suppository formulation

	<u>Per suppository</u>
Active ingredient (63 $\mu$ m)*	250 mg
Hard Fat, BP (Witepsol H15 - Dynamit Nobel)	<u>1770</u> mg
	2020 mg

\* The active ingredient is used as a powder wherein at least 90% of the particles are of 63 $\mu$ m diameter or less.

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at a maximum temperature of 45°C. The active ingredient is sifted through a 200 $\mu$ m sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension which is stirred until homogenous. The entire suspension is then passed through a 250 $\mu$ m stainless steel screen and allowed to cool to 40°C with continuous stirring. At a temperature of 38-40°C, 2.0g aliquots of the mixture are filled into suitable plastic moulds and the suppositories allowed to cool to room temperature.

Pessary formulation

	<u>Per pessary</u>
Active ingredient (63 $\mu$ m)	250 mg
Anhydrous Dextrose	380 mg
Potato Starch	363 mg
Magnesium Stearate	<u>7</u> mg
	1000 mg

The ingredients are mixed directly and pessaries prepared by compression of the resulting mixture.



### Biological Assays

#### (i) In vitro assay for the inhibition of ACAT activity

ACAT activity was determined as described by Ross *et al* by the incorporation of [ $^{14}$ C]oleoyl-CoA into cholesterol [ $^{14}$ C]oleate using hepatic microsomes as the source of both ACAT and cholesterol. Microsomes were prepared from the livers of male CD rats fed a 0.4% cholesterol/0.2% cholic acid diet 3.5 days before sacrifice. Various concentrations of a test compound were preincubated with a 0.5mg/ml microsomal suspension and after 15 minutes a 50 $\mu$ g aliquot was removed and incubated with 25 $\mu$ M of [ $^{14}$ C]-enriched oleoyl-CoA for 4 minutes. The reaction was terminated by the addition of 1ml of ethanol and 4ml of hexane. After shaking, the hexane layer was removed and evaporated to dryness. The hexane extract was then reconstituted in 150 $\mu$ l of HPLC solvent and injected on to a B&J OD5 Reverse Phase C18 column using an isocratic mobile phase of acetonitrile: isopropanol:heptane (50:40:10) in 0.5% acetic acid at a flow rate of 1.0ml/min. The product of the reaction, [ $^{14}$ C]oleoyl cholesterol, was measured using a Flow One radiometric detector. The ACAT IC<sub>50</sub> value for each compound was determined from a plot of % inhibition from control vs inhibitor concentration.

The IC<sub>50</sub>s for the compounds of Synthetic Examples 1 to 3 were 4.5 $\mu$ M, 3.4 $\mu$ M and 7.6 $\mu$ M respectively.

#### (ii) Determination of hypolipidemic activity in cholesterol-cholic acid fed rats

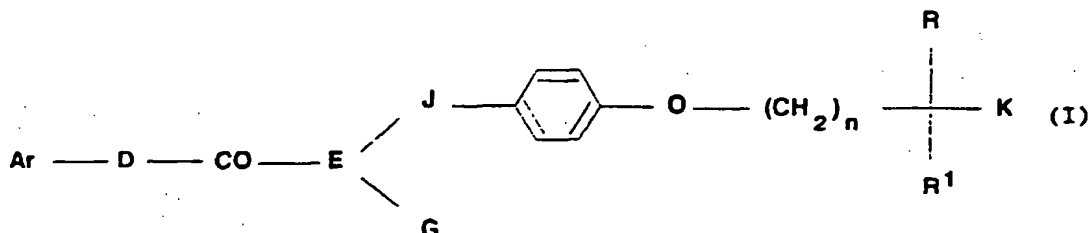
Male Sprague-Dawley rats (CD, Charles River) each weighing 200-300g were used. Hypercholesterolemia was induced in the rats by administration of a diet enriched to 0.4% cholesterol, 0.2% cholic acid. Prior to the administration of the diet, blood samples were collected under halothane anesthesia by cardiac

puncture to determine baseline lipid levels. The blood was allowed to clot and serum was obtained for the analysis of total cholesterol, dextran-precipitable lipoproteins cholesterol (VLDL + LDL) and total triglycerides. The rats were divided into groups so that each group had similar average baseline serum lipid levels. Five days after the initial blood sampling, administration of each test compound and the cholesterol-cholic acid-enriched diet was begun. Compounds to be tested by gavage were administered b.i.d. in either 0.5% methyl cellulose or 5% sodium bicarbonate at 9:00 a.m. and 3:00 p.m. for three days and at 9:00 a.m. on the fourth day. Compounds administered as part of the diet were dissolved in ethanol and sprayed on to the diet. The ethanol was allowed to evaporate and the diet given to the rats for three days. On the fourth day, blood samples were collected and the final serum lipid levels determined. All blood samplings were taken after a four-hour fast.

The compound of Synthetic Example 1 at a dose of 25mg/kg reduced LDL-cholesterol by 55% and at a dose of 50mg/kg by 67%. The corresponding figures for the compound of Synthetic Example 2 were 5mg/kg (41-71%) and 25mg/kg (61%) and for the compound of Synthetic Example 3 were 0.5mg/kg (90%) and 2mg/kg (74%).

CLAIMS

1. A compound of formula (I)



wherein

Ar is a mono- or bicyclic aromatic group optionally containing one or two heteroatoms independently selected from nitrogen, oxygen and sulphur, said group being optionally substituted by one or more atoms or groups independently selected from halogen, nitro, amino,  $-\text{NRR}^1$  where R and  $\text{R}^1$  are independently selected from hydrogen,  $\text{C}_{1-8}$  alkyl and  $\text{C}_{1-8}$  alkanoyl, cyano, carboxyalkoxy, alkoxycarbonylalkoxy,  $\text{C}_{1-8}$  alkyl (including cycloalkyl and cycloalkylalkyl),  $\text{C}_{1-8}$  alkoxy (including cycloalkoxy and cycloalkylalkoxy),  $\text{C}_{1-8}$  thioalkyl, said alkyl, alkoxy and/or thioalkyl group(s) being optionally substituted by one or more halogen atoms, aryl, aryloxy, aralkyl and aralkyloxy, said aryl, aryloxy, aralkyl and/or aralkyloxy group(s) being optionally substituted by one or more atoms or groups independently selected from halogen, alkyl, alkoxy, alkanoyl, hydroxyalkyl, perfluoroalkyl, perfluoroalkoxy, carboxyalkoxy, alkoxycarbonylalkoxy, and  $\text{C}_{3-8}$  polyether groups containing from one to three oxygen atoms;

D is  $-\text{CH}_2-$ ,  $-\text{NH}-$ , or  $-\text{O}-$ ;

E is  $-\text{N}<$  or  $-\text{CH}<$ ;

G is hydrogen, C<sub>1-12</sub> straight, branched, or cyclic alkyl, or aralkyl, said aralkyl group being optionally substituted by one or more atoms or groups independently selected from halogen, amino, N-(C<sub>1-6</sub> alkyl)amino, N,N-di(C<sub>1-6</sub> alkyl)amino, C<sub>1-6</sub> alkyl and C<sub>1-6</sub> alkoxy, or a C<sub>3-8</sub> polyether group containing one to three oxygen atoms;

J is a bond or C<sub>1-6</sub> straight or branched alkylene;

n is an integer of from 0 to 10;

R and R<sup>1</sup> are as hereinbefore defined; and

K is -CH<sub>2</sub>OH, -CHO, -CONHCH<sub>2</sub>CONH<sub>2</sub>, -CONH(C<sub>1-6</sub> alkyl), -OC(C<sub>1-4</sub> alkyl)<sub>2</sub>OCOHeteroaryl, -CO<sub>2</sub>R<sup>2</sup> where R<sup>2</sup> is hydrogen, C<sub>1-8</sub> alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or a C<sub>3-8</sub> polyether group containing from one to three oxygen atoms, or -CONHAr' where Ar' is phenyl optionally substituted by one or more atoms or groups selected from fluorine, nitro, -NRR<sup>1</sup> where R and R<sup>1</sup> are as hereinbefore defined, C<sub>1-6</sub> alkyl and C<sub>1-6</sub> alkoxy, said alkyl and/or alkoxy group(s) being optionally substituted at the terminal carbon by -CO<sub>2</sub>R<sup>3</sup> where R<sup>3</sup> is C<sub>1-6</sub> alkyl;

and salts and physiologically functional derivatives thereof.

2. A compound of formula (I) as shown in Claim 1, wherein

Ar is phenyl or naphthyl substituted by one or more atoms or groups independently selected from halogen, C<sub>1-8</sub> alkyl, C<sub>1-8</sub> alkoxy (including cycloalkylalkoxy), said alkyl and/or alkoxy group(s) being optionally substituted by one or more halogen atoms, C<sub>1-8</sub> thioalkyl, aryl, aryloxy and aralkoxy, said aralkoxy group being optionally substituted by alkyl, alkoyl, or hydroxyalkyl;

D is -NH- or -O-;

E is -N<;

G is C<sub>5-8</sub> straight or branched alkyl, (4-halophenyl)C<sub>1-3</sub> alkyl, or [4-di(C<sub>1-6</sub> alkyl)aminophenyl]C<sub>1-3</sub> alkyl;

J is C<sub>1-3</sub> alkylene;

n is an integer of from 0 to 4;

R and R<sup>1</sup> are respectively hydrogen and C<sub>1-4</sub> alkyl or are both C<sub>1-4</sub> alkyl; and

K is -CO<sub>2</sub>R<sup>2</sup> where R<sup>2</sup> is hydrogen or C<sub>1-4</sub> alkyl, or -CH<sub>2</sub>OH;

and salts and physiologically functional derivatives thereof.

3. A compound of formula (I) as claimed in Claim 1, which compound is selected from

2-(4-(2-[3-(2,4-dimethoxyphenyl)-1-heptylureido]ethyl)phenoxy)-2-methylpropionic acid,

2-(4-(2-[3-(2,4-difluorophenyl)-1-heptylureido]ethyl)phenoxy)-2-methylpropionic acid;

2-(4-[3-(2,4-dimethoxyphenyl)-1-heptylureidomethyl]phenoxy)-2-methylpropionic acid,

2-(4-[1-heptyl-3-(2,4,6-trichlorophenyl)ureidomethyl]phenoxy)-2-methylpropionic acid,

2-(4-[1-(3,3-dimethylbutyl)-3-(2,4-dimethoxyphenyl)ureidomethyl]-phenoxy)-2-methylpropionic acid,

3-(2,4-dimethoxyphenyl)-1-heptyl-1-[4-(2-hydroxy-1-methylethoxy)benzyl]urea,

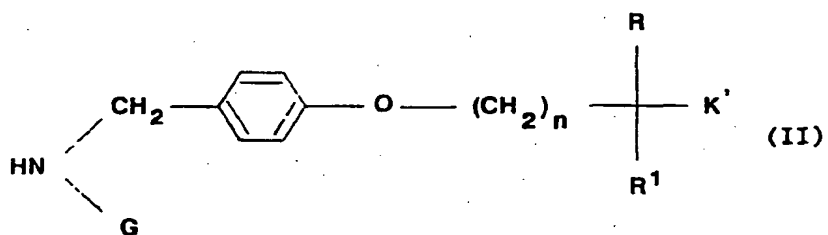
3-(2,4-dimethylphenyl)-1-heptyl-1-[4-(5-hydroxy-4,4-dimethylpentyloxy)benzyl]urea

and their physiologically acceptable salts and physiologically functional derivatives.

4. A compound of formula (I) as claimed in any of Claims 1 to 3, or a physiologically functional derivative thereof, for use as a therapeutic agent.
5. A compound of formula (I) as claimed in any of Claims 1 to 3, or a physiologically functional derivative thereof, for use in the prophylaxis or treatment of a clinical condition for which an ACAT inhibitor and/or a fibrate is indicated.
6. A compound of formula (I) as claimed in any of Claims 1 to 3, or a physiologically functional derivative thereof, for use in the prophylaxis or treatment of atherosclerosis.
7. Use of a compound of formula (I) as claimed in any of Claims 1 to 3, or of a physiologically functional derivative thereof, in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which an ACAT inhibitor and/or a fibrate is indicated.
8. Use of a compound of formula (I) as claimed in any of Claims 1 to 3, or of a physiologically functional derivative thereof, in the manufacture of a medicament for the prophylaxis or treatment of atherosclerosis.
9. A method for the prophylaxis or treatment of a clinical condition for which an ACAT inhibitor and/or a fibrate is indicated which

comprises the administration of a therapeutically effective amount of a compound of formula (I) as claimed in any of Claims 1 to 3 or of a physiologically functional derivative thereof.

10. A method as claimed in Claim 9 for the prophylaxis or treatment of atherosclerosis.
11. A medicament comprising a compound of formula (I) as claimed in any of Claims 1 to 3, or a physiologically functional derivative thereof, a pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents for use in the prophylaxis or treatment of a clinical condition for which an ACAT inhibitor and/or a fibrate is indicated.
12. A medicament as claimed in Claim 11 for use in the prophylaxis or treatment of atherosclerosis.
13. A medicament as claimed in Claim 11 or 12 which is in the form of a tablet or capsule.
14. A process for the preparation of a compound of formula (I) as claimed in Claim 1 which comprises reacting a compound of formula (II)



wherein n, G, J, R and R<sup>1</sup> are as defined in Claim 1 and K' is as defined for K in Claim 1 or is a suitably protected form thereof, with a compound of formula (III)



wherein Ar is as defined in Claim 1,

and, if necessary, deprotecting the product.

15. A method for the preparation of a medicament as claimed in Claim 11 or 12 which comprises

(a) preparing a compound of formula (I) or a physiologically functional derivative thereof by a process as claimed in Claim 14; and

(b) admixing the product from step (a) with a pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents.

16. A method as claimed in Claim 15 which comprises an additional step (c) wherein the admixture from step (b) is formed into a tablet or capsule.
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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 91/02195

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5                      C 07 C 275/34                      C 07 C 275/30                      C 07 C 275/28 A 61 K 31/19                      A 61 K 31/17                      C 07 C 273/18		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.C1.5	C 07 C	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	US,A,4623662 (DE VRIES) 18 November 1986 ---	
A	US,A,4397868 (DE VRIES) 9 August 1983 ---	
A	US,A,4387106 (DE VRIES et al.) 7 June 1983 ---	
A	EP,A,0370740 (THE WELLCOME RESEARCH LABORATORIES) 30 May 1990 -----	
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents :</p> <p><sup>A</sup> document defining the general state of the art which is not considered to be of particular relevance</p> <p><sup>E</sup> earlier document but published on or after the international filing date</p> <p><sup>L</sup> document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p><sup>O</sup> document referring to an oral disclosure, use, exhibition or other means</p> <p><sup>P</sup> document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p><sup>T</sup> later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p><sup>X</sup> document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p><sup>Y</sup> document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p><sup>&amp;</sup> document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
10-03-1992	07 APR 1992	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	Mme N. KUIPER	

## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE <sup>1</sup>

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers                      because they relate to subject matter not required to be searched by this Authority, namely:  
 Remark: Although claims 4-6,9-10 are directed to a method of treatment of human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☒ Claim numbers 1-2,4-16 (incompletely) because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically  
 As formula (1) in claim 1 only contains a minor fixed part and considering the large number of variables, which may also contain variables, the scope of said claim cannot be evaluated and an exhaustive search is thus impossible. The search has been based on the explicitly claimed compounds. For the same reason it could be that this application does not fulfill the requirements of Art.6 PCT (clearness of claims) and of rule 13.1 PCT (single invention concept)
3. ☐ Claim numbers                      because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING <sup>2</sup>

This International Searching Authority found multiple inventions in this international application as follows.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

## Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest
- ☐ No protest accompanied the payment of additional search fees

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9102195

SA 54108

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 26/03/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4623662	18-11-86	US-A- 5003106	26-03-91
US-A- 4397868	09-08-83	None	
US-A- 4387106	07-06-83	None	
EP-A- 0370740	30-05-90	AU-A- 4536389	24-05-90
		EP-A- 0450660	09-10-91
		JP-A- 2188568	24-07-90

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